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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
VENCI, DAVID J	

ART UNIT	PAPER NUMBER
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/733,617	XU ET AL.	
	Examiner	Art Unit	
	DAVID J. VENCI	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *March 18, 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *9-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-31* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Examiner acknowledges Applicants' Arguments/Remarks Amendment and Notice of Appeal, both filed November 30, 2007. Applicants' Arguments/Remarks Amendment was entered in the Office Advisory Action dated December 27, 2007. However, the finality of the Final Rejection dated May 17, 2007, is withdrawn because it was principally determined that the Office Advisory Action dated December 27, 2007, improperly did not address all Applicants' arguments presented in Applicants' reply filed November 30, 2007 (see PTOL-413 – Interview Summary of interview of March 11, 2007, and PTOL-413 – Interview Summary of interview of February 8, 2008).

New grounds of rejection under 35 U.S.C. 103(a) in view of Campbell (US 2,957,808) and Nock & Sydor (US 2002/0049152) are set forth *infra*. Reconsideration is respectfully requested.

Claims 1-31 are pending in this application. Claims 9-31 are directed to non-elected inventions and were withdrawn from consideration in the Office Action dated February 28, 2005.

Claims 1-8 are under examination.

Specification

The disclosure is objected to because of the following informalities:

On p. 30, paragraph beginning on line 9, third sentence, the phrase "reactive C-terminal thioester on one of the carrier or ligand is the product of intein cleavage in the presence of a thiol reagent" is not clear in view of Figure 1. According to Fig. 1, an "N-S acyl shift" generates a C-terminal thioester that pre-exists "intein cleavage in the presence of a thiol reagent" (see also, PTOL-413 – Interview Summary of February 8, 2008, Applicant Tom Evans acknowledged what appears to be a C-terminal

thioester attached to the second chitin bead from the top of Figure 1). Furthermore, according to Applicants' specification Fig. 1, "2-mercaptoethanesulfonic acid" cleaves said "carrier-intein fusion protein" to generate an N-terminal cysteine (*i.e.*, not the claimed "C-terminal thioester").

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, step a), the terms "intein" and "carrier-intein fusion protein" are indefinite. According to Applicants' specification, an "intein" is a "self-splicing protein" (see Specification, p. 20, lines 5-8). However, Examiner is unable to correspond a "self-splicing protein" to any object in claim 1. Furthermore, Examiner is unable to discern any "self-splicing" step anywhere in claim 1. Whether "2-mercaptoethanesulfonic acid" effectuates "self-splicing" is not clear. Clarification is required.

In claim 1, step a), the phrase "wherein a carrier-intein fusion protein is cleaved in the presence of 2-mercaptoethanesulfonic acid to generate the C-terminal thioester" is indefinite. Figure 1. According to Fig. 1, an "N-S acyl shift" generates a C-terminal thioester that pre-exists "intein cleavage in the presence of a thiol reagent" (see also, PTOL-413 – Interview Summary of February 8, 2008, Applicant Tom Evans acknowledged what appears to be a C-terminal thioester attached to the second chitin bead from the top of Figure 1). Furthermore, according to Applicants' specification Fig. 1, "2-mercaptoethanesulfonic acid"

cleaves said "carrier-intein fusion protein" to generate an N-terminal cysteine (*i.e.*, not the claimed "C-terminal thioester"). Clarification is required.

In claim 1, step b), the second instance of the phrase "the carrier-ligand conjugate" lacks antecedent basis and/or is indefinite. Whether step b) requires two "carrier-ligand conjugate" fractions, or whether the "carrier-ligand conjugate" referenced in the step of "contacting the carrier-ligand conjugate with a mixture" is the anteceding matrix-bound "carrier-ligand conjugate" is not clear.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell (US 2,957,808) in view of Nock & Sydor (US 2002/0049152).

Campbell describes a method for purifying a ligand-binding molecule from a mixture, the method comprising the steps:

(c) adding matix-bound carrier-ligand conjugates to a mixture containing a ligand-binding molecule (see col. 1, lines 41-46, "the antibody or antigen specific to the selected material may be combined specifically with the insolubilized material to give complexes[...]"); and

(d) changing conditions to elute the ligand-binding molecule from the matix-bound carrier-ligand conjugates, thereby obtaining purified ligand-binding molecule (see col. 1, lines 41-46, "[...] to give complexes that can be disassociated into easily separable soluble antigen or antibodies and insoluble material"; see *e.g.*, col. 3, lines 49-50, "The pH was then adjusted to approximately 3.2 with 0.1 N HCl to dissociate the antibody"; see *also*, lines 52-54, "The insoluble antigen-cellulose complex was removed by centrifugation, leaving the antibody in solution").

Campbell does not describe a method incorporating steps of adding 2-mercaptoethanesulfonic acid to a thioester on a carrier protein to form carrier-ligand conjugates, or adding the carrier-ligand conjugates to a matrix, wherein the carrier-ligand conjugates are intended to bind non–covalently to the matrix, to form matix-bound carrier-ligand conjugates.

However, Nock & Sydor describe:

(a) adding 2-mercaptoethanesulfonic acid (see *e.g.*, para. [0059], "Suitable activating compounds that have nucleophilic groups include[...] 2-mercaptoethanesulfonic acid") (paraphrasing mine) to a thioester on a carrier protein (see *e.g.*, para. [0059], "The activating compound then becomes attached to the end of the extein that was adjacent to the intein by a thioester or ester bond"; see *also*, para. [0057], "This intermediate then undergoes a trans-esterification reaction due to nucleophilic attack by an O or S-containing side chain of a Cys, Ser or Thr residue at the C-terminal end of the intein"), thereby forming carrier-ligand conjugates;

(b) adding the carrier-ligand conjugates of step a) to a matrix, wherein the carrier-ligand conjugates are intended to bind non–covalently to the matrix, thereby forming matix-bound carrier-ligand conjugates (see paragraph [0094], "the peptide can include a tag which can non-covalently associate with a molecule that is attached to a surface");

It would have been obvious for persons of ordinary skill to upgrade Campbell's purification method with a Nock- & Sydor-type linker construct because Nock's & Sydor's linker has both purification and immobilization functions (see para. [0065], "Such tags are useful in the purification of the resulting polypeptide by affinity binding prior to immobilization on the array. Tags can also be used to attach the polypeptides to the surface to form arrays"). In addition, Nock's & Sydor's intein-catalyzed splicing chemistry allows for complete removal and/or modular exchange of linkers with a variety of other linkers (see para. [0066]).

Thus, Nock's & Sydor's linker affords Campbell increased flexibility and method design choice for purifying ligand-binding molecules (see Nock & Sydor, para. [0135], Arrays of surface-attached polypeptide species that are obtained using the methods of the invention are typically screened to identify those that have a desired activity (e.g., binding affinity to a target molecule of interest)"; see also, para. [0136], "The present invention also provides transferring the target molecule to a reaction chamber(s) that, in one embodiment, provides solutions or condition (e.g. elevated temperature) that dissociates the target molecule from the affinity molecule").

With respect to claims 2 and 7, Campbell describes ligand-binding molecules that are antibodies from an antiserum (see col. 1, lines 20-24, "antibodies and antigens from serums from immune animals and humans").

With respect to claims 3-7, Nock & Sydor describe a matrix-binding protein, carbohydrate-binding domain, or a chitin-binding domain (see para. [0066], "chitin binding domain") which binds chitin.

Response to Arguments

Claim Rejections - 35 USC § 112

"intein" and "carrier-intein fusion protein"

In prior Office Action, claim 1 was rejected under 35 U.S.C. 112, second paragraph, because the terms "intein" and "carrier-intein fusion protein" are indefinite. According to Applicants' specification, an "intein" is a "self-splicing protein" (see Specification, p. 20, lines 5-8). However, Examiner is unable to correspond a "self-splicing protein" to any object in claim 1. Furthermore, Examiner is unable to discern any "self-splicing" step anywhere in amended claim 1. Whether "2-mercaptoethanesulfonic acid" effectuates "self-splicing" is not clear.

In response, Applicants appear to argue:

1. The claimed method requiring a self-splicing "intein" protein is not indefinite because the claim also requires thiol reagents to inhibit splicing or completion of splicing (see Applicants' reply, filed November 30, 2007, p. 8, last two paragraphs).
2. The claimed method requiring a self-splicing "intein" protein is not indefinite because mutations within native inteins inhibit splicing or completion of splicing, and the specification definition of "intein" includes such mutated inteins provided by New England Bioloabs, Inc. (see Applicants' reply, filed November 30, 2007, p. 8, penultimate paragraph and p. 9, first paragraph).

Applicants' arguments have been carefully considered but are not persuasive. With respect to argument 1), the language of claim 1 does not make clear that the claimed "intein" is NOT undergoing self-splicing, contrary to one's expectation in view of the specification and prior art definition of "intein" as being a "self-splicing protein". Furthermore, Applicants' suggestion that thiol reagents inhibit splicing or completion of splicing does not appear consistent with the specification Fig. 1, wherein the added thiol reagent "$^{-}SO_3$-

CH_2-CH_2-SH" splices onto the C-terminal thioester of the carrier protein (see Fig. 1, second step, “MESNA induced cleavage”).

With respect to argument 2), the specification and prior art makes clear that an "intein" is *any* “self-splicing protein” (see Specification, p. 20, lines 5-8) and is not limited to specific mutants defined at New England Bioloabs, Inc. Thus, the scope of Applicants’ argument is not commensurate in scope to the claimed invention because the claims merely recite an "intein" (*i.e.*, a “self-splicing protein”), and the language of claim 1 does not make clear that the claimed “intein” is NOT undergoing self-splicing, contrary to one’s expectation in view of the specification and prior art definition of “intein” as being a “self-splicing protein”.

“wherein a carrier-intein fusion protein is cleaved in the presence of 2-mercaptoethanesulfonic acid to generate the C-terminal thioester”

In prior Office Action, claim 1 was rejected under 35 U.S.C. 112, second paragraph, because the phrase “wherein a carrier-intein fusion protein is cleaved in the presence of 2-mercaptoethanesulfonic acid to generate the C-terminal thioester” is indefinite. According to Fig. 1, an “N-S acyl shift” generates a C-terminal thioester that pre-exists “intein cleavage in the presence of a thiol reagent” (see also, PTOL-413 – Interview Summary of interview of February 8, 2008, Applicant Tom Evans acknowledged what appears to be a C-terminal thioester attached to the second chitin bead from the top of Figure 1). Furthermore, according to Applicants’ specification Fig. 1, “2-mercaptoethanesulfonic acid” cleaves said “carrier-intein fusion protein” to generate an N-terminal cysteine (*i.e.*, not the claimed “C-terminal thioester”).

In response, Applicants argue that “[t]he formation of a C-terminal thioester on the carrier protein is the result of cleavage of an intein fusion protein in the presence of a thiol reagent” (see Applicants’ reply, filed November 30, 2007, p. 9, second paragraph, second sentence).

This argument is not persuasive because the C-terminal thioester attached to the second chitin bead from the top of Figure 1 is not generated by a cleavage event, as claimed, but pre-exists the cleavage event. Thus, the claimed phrase "wherein a carrier-intein fusion protein is cleaved in the presence of 2-mercaptoethanesulfonic acid to generate the C-terminal thioester" is indefinite.

Claim Rejections - 35 USC § 102

In prior Office Action, claims 1-8 were rejected under 35 U.S.C. 102(e) as being anticipated by Nock & Sydor (US 2002/0049152).

This rejection is withdrawn in lieu of new grounds of rejection under 35 U.S.C. 103(a) in view of Campbell (US 2,957,808) and Nock & Sydor (US 2002/0049152) as set forth *supra*. Reconsideration is respectfully requested.

Applicants' arguments as applied to the noted differences between the teachings of the present application and the teachings of Nock & Sydor (see Applicants' reply, filed November 30, 2007, Table at bottom of p. 11) do not distinguish Applicants' invention from the *combined* teachings of Campbell and Nock & Sydor.

Specifically, Applicants' argument that Nock & Sydor do not describe the claimed step of eluting ligand-binding molecules (see Applicants' reply, filed November 30, 2007, Table at bottom of p. 11, last row, "No elution step described. Only immobilization") is not persuasive because Campbell discovered that simply lowering pH is useful for eluting proteins from cellulose resins (see Campbell, col. 3, lines 49-50, "The pH was then adjusted to approximately 3.2 with 0.1 N HCl to dissociate the antibody"; see *also*, lines 52-54, "The insoluble antigen-cellulose complex was removed by centrifugation, leaving the antibody in solution").

It would have been obvious for persons of ordinary skill to upgrade Campbell's purification method with a Nock- & Sydor-type linker construct because Nock's & Sydor's linker has both purification and immobilization functions (see para. [0065], "Such tags are useful in the purification of the resulting polypeptide by affinity binding prior to immobilization on the array. Tags can also be used to attach the polypeptides to the surface to form arrays"). In addition, Nock's & Sydor's intein-catalyzed splicing chemistry allows for complete removal and/or modular exchange of linkers with a variety of other linkers (see para. [0066]).

Conclusion

No claims are allowable at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Venci whose telephone number is (571)272-2879. The examiner can normally be reached on 08:00 - 16:30 (EST). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

David J Venci
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/Long V Le/
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